Office de la propriété intellectuelle du Canada
Un organisme d'Industrie Canada
www.opic.gc.ca

Canadian Intellectual Property Office
An Agency of Industry Canada
www.cipo.gc.ca

August 16, 2005

G. RONALD BELL & ASSOCIATES
P.O. Box 2450, Postal Station D
1215 - 99 Bank Street
OTTAWA Ontario
K1P 5W6

Application No.	:	**2,349,810**
Owner	:	MORISAWA, SHINKATSU; WANG, XIAO BING
Title	:	**ISOMETRIC PRIMER EXTENSION METHOD AND KIT FOR DETECTION AND QUANTIFICATION OF SPECIFIC NUCLEIC ACID**
Classification	:	C12Q-1/68
Your File No.	:	**84-397C**
Examiner	:	Qianfa (Kevin) Chen

YOU ARE HEREBY NOTIFIED OF A REQUISITION BY THE EXAMINER IN ACCORDANCE WITH SUBSECTION 30(2) OF THE *PATENT RULES*. IN ORDER TO AVOID ABANDONMENT UNDER PARAGRAPH 73(1)(A) OF THE *PATENT ACT*, A WRITTEN REPLY MUST BE RECEIVED WITHIN 6 MONTHS AFTER THE ABOVE DATE.

This application has been examined taking into account applicant's correspondence received in this office on September 22, 2004.

The number of claims in this application is 37.

A further search of the prior art has revealed the following:

References Re-Applied:

Patent Document WO 96/30545	October 3, 1996		Fahy et al.
Non-Patent Document Human Mutation	1992	Vol. 1 (2), Pages 159-164	Prezant et al.

New Reference Applied:

Book Document
Protocols and Applications Guide, 2nd Edition, March 1991, Pages 84-85 Promega

Fahy et al. describe a method for detecting or quantifying a target nucleic acid wherein the method is based on polymerase-directed extension of an oligonucleotide primer using selected mixtures of up to three nucleotide triphosphates and one or more chain terminating, base pairing entities, such as dideoxynucleotide triphosphates (page 6, lines 31-36). Fahy et al. also describe a method for simultaneously determining the presence of at least two related polynucleotides (e.g., a wild-type and a mutant gene). The method includes a) hybridizing a primer to each of the related polynucleotides at a position that is proximal and 3' to the point of the deviation between the related polynucleotides, b) extending the primer in the presence of a mixture that contains either i) two or three dNTP and no chain terminating, base pairing entities, or ii) one to three dNTPs and one chain-terminating base-paring entities (page 16, lines 17-28). The nucleotide used for extension or chain termination include detection moieties (page 21, lines 27-31). Synthesis of the extension products is accomplished by polymerase extension of the primers until a template nucleotide is read or omitted which terminates synthesis. For example, a nucleotide in the template can be read for which no complementary dNTP is available in the extension mixture, resulting in chain termination. Or, more preferably, a nucleotide in the template can be read for which a complementary chain terminating, base pairing entities is available, likewise resulting in chain termination (page 19, lines 8-17). The method is typically used in connection with a genetic mutation within a gene. However, the method is useful in any instance where related polynucleotides are to be analysed (page 17, lines 1-5). The method can be used for accurately quantifying the prevalence of a mutation in a background of a normal gene sequence (page 1, lines 7-9).

Prezant et al. describe a method for screening point mutation (i.e., detecting a target nucleic acid) by hybridizing a 5'-biotinylated primer to the target, extending the primer in the presence of one radioactive labelled dNTP and a DNA polymerase, and in the absence of any ddNTPs.

Promega describes a method for detecting the nucleotide sequence of a DNA or RNA template. The method is based on a primer extension reaction wherein the primer is annealed to the DNA or RNA template prior to the reaction components and enzymes being added to the reaction tube.

The examiner has identified the following defects in the application:

Claim 1 and the claims dependent thereon do not comply with Paragraph 28.2(1)(b) of the Patent Act. Fahy et al. disclosed the claimed subject matter before the claim date.

In his response dated September 22, 2004 to a similar objection under 28.2(1)(b) made in the examiner's action of March 22, 2004, applicant argued that "the cited reference does not constitute a direct anticipation of any one of the claims". Applicant's comments have been carefully considered but have not been persuasive.

First, applicant argued that "the cited prior art reference relies on PCR technology to synthesize products, which increases the cost of each experiment and uses more laboratory space then the method of the present invention". The method of Fahy et al. is based on a primer extension reaction and the method of claim 1of the instant application is also based on a primer extension reaction. It is unclear how the primer extension reaction of Fahy et al. is different from the primer extension reaction of claim 1 of the instant application. Applicant's attention is drawn to claim 12 of the instant application which defines that "The method according to claim 1, the target nucleic acid is synthesized by polymerase chain reaction" (PCR technology). Second, applicant argued that "the cited prior art reference includes primers in the reaction mixture" while in the present invention "primers are annealed to the template in a separate step". Applicant's attention is drawn to page 16, lines 20-28 of the description of Fahy et al. where primers are annealed to the template in step a) (a separate step) prior to the reaction components being added in step b). Third, applicant argued that the method of Fahy et al. is "only applicable to studying genetic mutation" while the present invention is "ideally suited to study not only genetic mutations..., but the products can be readily quantified for studies on gene expression". However, a method for detecting genetic mutation falls within the scope of the method for detecting a target nucleic acid in a sample as defined in claim 1. Finally, applicant argued that the cited prior art reference "can only reliably qualify the presence or absence of a genetic mutation and cannot be modified to quantify levels of mRNA or DNA". The method of Fahy et al. comprises all the technical features (method steps and reagents being used in each step) and therefore the method of Fahy et al. is inherently useful for quantifying levels of mRNA or DNA. Applicant's attention is drawn to page 17, lines 1-8 of the description of Fahy et al. which indicates that "The method of the present invention is typically used in connection with a genetic mutation within a gene. However, the method of the invention is useful in any instance where related polynucleotides are to be analysed". Applicant's attention is further drawn to page 1, lines 7-9 of the description of Fahy et al. which indicates that "the invention provides for a method of accurately quantifying the prevalence of a mutation in a background of a normal gene sequence". A method for quantifying a genetic mutation falls within the scope of the method for quantifying a target nucleic acid in a sample as defined in claim 1.

In view of the foregoing, a novelty for claim 1 and the claims dependent thereon cannot be acknowledged.

Claim 1 and the claims dependent thereon do not comply with section 28.3 of the *Patent Act*. The subject matter of these claims, when the method is used for detecting a target nucleic acid in a sample and when method step (c)(1) is carried out, would have been obvious on the claim date to a person skilled in the art or science to which they pertain having regard to Prezant et al. and Promega.

Prezant et al. describe a method for screening point mutations (i.e., detecting a target nucleic acid) by hybridizing 5'-biotinylated primers to the target, extending the primer in the presence of a radioactive dNTP (i.e., one type of free non-terminator nucleotides wherein at least one type of non-terminator nucleotide is labelled with a detectable marker), and in the absence of any terminator ddNTP nucleotides (page 10, lines 5-10 and Figure 1). Prezant et al. do not describe that the primers are annealed to the template in a separate step. However, in a primer extension reaction or in a polymerase chain reaction, annealing a primer to a target in a separate step prior to other reaction components (dNTPs and enzymes) being added to the reaction is a well-known technique in the art in order to increase the binding strength of the primer without fear of inactivating enzymes or damaging components. For example, Promega describes a method for detecting nucleotide sequence. The method is based on a primer extension reaction wherein the primer is annealed to the DNA or RNA template prior to the reaction components and enzymes being added to the reaction tube (page 85, method steps B1-B3, D1-D7 and E1-E7). Therefore, it would be obvious to a person skilled in the art, in order to increase the binding strength of the primer without fear of inactivating enzymes or damaging components, to substitute the method step of Prezant et al. (i.e., primer being added together with other reaction components) for the method step of Promega (i.e., primer being annealed to the target in a separate step prior to other reaction components being added to the reaction) thereby arriving at the subject matter of claim 1.

In view of the foregoing defects, the applicant is requisitioned, under subsection 30(2) of the *Patent Rules*, to amend the application in order to comply with the *Patent Act* and the *Patent Rules* or to provide arguments as to why the application does comply.

Qianfa (Kevin) Chen
Patent Examiner, Ph.D.
(819) 994-1374
2349810A.qkc